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Menopause and lead body burden among US women aged 45–55, NHANES 1999–2010

Pauline Mendola¹, Kate Brett², Jessica N. DiBari³, Anna Z. Pollack¹, Rashmi Tandon², and Edmond D. Shenassa³

¹Epidemiology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 6100 Executive Blvd, Rockville, MD 20852

²CDC/National Center for Health Statistics, 3311 Toledo Road, Hyattsville, MD 20782

³Maternal and Child Health Program, Department of Family Science, School of Public Health, University of Maryland, College Park, MD 20742

Abstract

Background—Environmental factors in menopause have received limited attention. Lead is a known reproductive toxicant associated with delayed puberty in girls that may also affect menopause.

Methods—The odds of menopause among US women aged 45–55 were estimated in the National Health and Nutrition Examination Survey, 1999–2010, in relation to quartiles of blood lead. Women still menstruating (n=2158) were compared to women with natural menopause (n=1063). Logistic regression models included age, race/ethnicity, current hormone use, poverty, smoking and where available, bone density or bone alkaline phosphatase.

Results—Lead levels (ug/dL) were higher in menopausal women, geometric mean (standard error) = 1.71 (0.04) vs. 1.23 (0.02). Adjusted odds of menopause and 95% confidence intervals for lead quartiles (lowest quartile referent) were 1.7 (1.0–2.8), 2.1 (1.2–3.6), and 4.2 (2.5–7.0) respectively. Results adjusting for bone markers were generally similar but had less precision.

Conclusions—Blood lead was associated with natural menopause in US women even after adjustment for bone turnover. This raises concern that lead exposure, even at low levels, may shorten women's reproductive lifespan.

Keywords

lead; menopause; women's health; epidemiology; environment

Corresponding Author: Dr. Pauline Mendola, Investigator, Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, 6100 Executive Blvd, Room 7B03F, Rockville, MD 20852, Phone: 301-496-5267, Fax: 301-402-2084, pauline.mendola@nih.gov.

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Human Subjects Review: Informed consent is obtained for all National Health And Nutrition Examination Survey participants and details of the study institutional review, approval and protocols for various years are found at: <http://www.cdc.gov/nchs/nhanes/irba98.htm>.

1. Introduction

Lead is a reproductive toxicant(Mendola, Messer, and Rappazzo, 2008) associated with delayed puberty(Selevan, Rice, Hogan, Euling, Pfahles-Hutchens, and Bethel, 2003;Wu, Buck, and Mendola, 2003) and alterations in reproductive hormones in peripubertal girls(Gollenberg, Hediger, Lee, Himes, and Louis, 2010) and in healthy premenopausal women.(Krieg, Jr., 2007;Krieg, Jr. and Feng, 2011;Pollack, Schisterman, Goldman, Mumford, Albert, Jones, and Wactawski-Wende, 2011) Prior studies report higher lead levels in postmenopausal women but they often draw from populations with higher exposure than currently observed, either because the data reflect past higher general population levels (Silbergeld, Schwartz, and Mahaffey, 1988;Symanski and Hertz-Picciotto, 1995) or because they target women with high lead exposures.(Garrido, Hernandez-Avila, Tamayo, bores Medina, Aro, Palazuelos, and Hu, 2003;Popovic, McNeill, Chettle, Webber, Lee, and Kaye, 2005;Potula, Kleinbaum, and Kaye, 2006) Even given today's lower levels, evaluating lead exposure in relation to menopause is challenging because circulating levels are influenced by increased bone turnover, which begins in perimenopause and significantly increases in early menopause.(Rabinowitz, 1991;Nash, Magder, Sherwin, Rubin, and Silbergeld, 2004)

While evidence suggests that lead exposure is associated with earlier menopause both in occupational cohorts(Popovic *et al.*, 2005) and primates,(Laughlin, Bowman, Franks, and Dierschke, 1987) there is a lack of data on this association in a nationally-representative sample of US women. Therefore, we examine the association of blood lead and menopause in the National Health and Nutrition Examination Survey (NHANES) 1999 – 2010.

2. Materials and Methods

The NHANES is a nationally-representative sample of the non-institutionalized civilian US population.(National Center for Health Statistics, 2012) Beginning in 1999, the NHANES is a continuous survey which results in a nationally-representative sample every two years. This analysis is based on six two-year cycles (1999–2010) and data were collected similarly in each cycle except where noted. Women 12 years old are asked about menstrual cycling in the past 12 months and those over 20 are asked reasons for not having a period in the past year. Lead was measured in whole blood using atomic absorption spectrometry in 1999–2002 (limit of detection (LOD) <0.6 ug/dL) and inductively coupled plasma mass spectrometry in 2003–2010 (LOD <0.25 ug/dL).

We selected women aged 45–55 years to cover a range of ages where menopause is likely to occur.(Brett and Cooper, 2003) Menopause was dichotomized: women with at least one menstrual cycle in the past 12 months were categorized as “No” (n=1144) and those with natural menopause were “Yes” (n=638). As such, perimenopausal women are grouped with premenopausal in comparison to women who are postmenopausal. Women who reported no menstrual period due to medical, surgical or other reasons (n = 787) were excluded.

We attempted to consider the impact of bone turnover during the perimenopausal period by adjusting for biologic markers where available. Bone alkaline phosphatase, a marker of bone turnover, was available from 1999–2002 (n = 515). We also adjusted for bone mineral density measured by dual energy x-ray absorptiometry, which was available in a comparable format for 2005–2008 (n = 541), to account for bone available for remodeling. Age, race/ethnicity and smoking were self-reported. Hormone replacement therapy (HRT) use was estimated based on self-reported use of estrogen containing pills or patches for menopause or menopausal symptoms. The poverty-to-income ratio was calculated based on family income and household composition relative to the poverty threshold.

The blood lead levels of women who were still menstruating are compared with women who reported a natural menopause. Quartiles of blood lead were based on all women in NHANES 1999–2010 aged 45–55. Logistic regression on menopausal status was adjusted for age, race/ethnicity, poverty and smoking. In separate models, we further adjusted for bone alkaline phosphatase in NHANES 1999–2002 and for femoral neck bone density in the 2005–2008 NHANES. Analyses were conducted in SAS (version 9.2) using SUDAAN (version 10.0) to account for the complex sampling design.

3. Results

Lead levels (ug/dL) were higher in menopausal women (geometric mean (standard error (SE)) = 1.71 (0.04)) compared to women still menstruating (geometric mean (SE) = 1.23 (0.02)). As expected, postmenopausal women were older but they were also less likely to be below the poverty line (Table 1).

Lead levels were associated with higher odds of menopause (Table 2). Using Q1 as the reference, adjusted odds ratios and 95% confidence intervals for Q2 through Q4 were 1.7(1.0–2.8), 2.1 (1.2–3.6), and 4.2 (2.5–7.0), respectively. While restriction to smaller subsamples with bone measures available decreased precision substantially, the overall relation between lead and menopause remained fairly similar. (Table 2).

4. Discussion

We find that menopause is associated with blood lead measures in US women at midlife, independent of markers of bone turnover. These findings build on prior studies of pubertal development,(Selevan *et al.*, 2003;Wu *et al.*, 2003;Gollenberg *et al.*, 2010) premenopausal hormone profiles,(Krieg, Jr., 2007;Krieg, Jr. *et al.*, 2011) and studies of ovarian function, (Taufeup, Poupon, Treton, Brosse, Richard, and Machelon, 2003) to suggest that lead shortens the reproductive lifespan of women, even at the very low levels observed in the past decade in the US.

Prior research has generally framed an alternative question – whether bone turnover creates a period of high lead levels around the menopausal transition. The extant data support an affirmative answer to that question even with remaining issues related to variability on the timing of maximum lead levels during the menopausal transition(Hernandez-Avila, Villalpando, Palazuelos, Hu, Villalpando, and Martinez, 2000) and despite methodologic challenges such as small sample sizes,(Popovic *et al.*, 2005;Potula *et al.*, 2006) combining natural and surgical menopause,(Popovic *et al.*, 2005) and examining a wide range of ages (e.g., women 20–85 years).(Symanski *et al.*, 1995;Jackson, Cromer, and Panneerselvamm, 2010)

Our primary interest is whether or not exposure to lead shortens the reproductive lifespan of women by delaying puberty and accelerating reproductive senescence. To date, only one study has reported on the timing of natural menopause associated with lead exposure, where former smelter workers had an earlier age at menopause (43.7 years) compared to a referent group of unexposed women (51.8 years), but the sample size is small (16 exposed women and 20 unexposed with natural menopause) and the exposures were high.(Popovic *et al.*, 2005) Our findings are consistent with this report, suggesting a relation between lead exposure, albeit at very reduced levels, and menopause in the general population.

Lead exposure has been associated with delayed puberty in girls (Selevan *et al.*, 2003;Wu *et al.*, 2003) possibly due to lower inhibin B, a marker for follicular development. (Gollenberg *et al.*, 2010) Ovulatory function may be disturbed, with increased follicle stimulating hormone (FSH) after lead exposure(Krieg, Jr., 2007;Krieg, Jr. *et al.*, 2011) (FSH is a key

indicator of ovarian reserve(Sherman, West, and Korenman, 1976)) as well as a phase shift with later progesterone peak in premenopausal women.(Pollack *et al.*, 2011) In addition, human ovarian granulosa cells retrieved from IVF candidates accumulated lead in culture and both messenger RNA and protein levels of cytochrome p450 and estrogen receptor beta(Taupeau *et al.*, 2003) were reduced suggesting down regulation that interferes with follicular function. Lead may alter hormonal expression via effects to the steroidogenic acute regulatory protein gene.(Srivastava, Dearth, Hiney, Ramirez, Bratton, and Dees, 2004) Animal studies also show accumulation of lead in the ovary leading to altered folliculogenesis in mice (Taupeau, Poupon, Nome, and Lefevre, 2001)and longer, irregular cycles in exposed Rhesus monkeys. (Laughlin *et al.*, 1987)

Despite a strong biologic rationale, longitudinal prospective data on this question are lacking. Approximately 95% of the body's lead burden is stored in the bone and the half-life of lead in blood in adults is 30–60 days.(Barry and Mossman, 1970) As such, current blood levels reflect overall body burden associated with long-term exposure as well as recent exposure and the release of lead from bone during periods of bone turnover. Periods of high bone turnover (pregnancy, lactation, menopause) are expected to correlate with a short-lived increase in blood lead(Silbergeld *et al.*, 1988) but the magnitude of change is dependent on lifetime exposure and accumulation and these relations are not always observed. For example, a recent report on NHANES 2003–2008 finds significantly lower blood lead levels among pregnant women compared to their non-pregnant counterparts.(Jones, Parker, and Mendola, 2010) Previous studies using NHANES data to evaluate lead and puberty have dealt with the issue of equilibration between blood and bone,(Wu *et al.*, 2003) since growth of long bones may sequester lead resulting in higher blood levels among shorter, pre-pubertal girls.(Selevan *et al.*, 2003) We attempt to address this important issue by adjusting for bone mineral density as a measure of current bone stores available for remodeling and a direct marker of bone turnover, bone alkaline phosphatase, and by restricting our sample to a plausible window for the menopausal transition. We also grouped perimenopausal women (who have high rates of bone turnover(Machida, Sun, Oguma, and Kayama, 2009)) with premenopausal women to provide more conservative estimates.

We restricted our analysis to women who were still menstruating or naturally menopausal to limit recall and did not rely on age at menopause which was often missing, implausibly reported or reported in 5-year age ranges. We focused on women around the time of the menopausal transition (ages 45–55) in order to dampen the impact of bone turnover which begins in the perimenopausal years and accelerates in early menopause.(Silbergeld *et al.*, 1988) Our analysis was limited by a substantial loss of precision in the subgroups with bone marker data available. Increasing the sample to include women aged 40 to 59 years provided similar results (data not shown). Given the wide confidence limits, the increased point estimates from 2005–2008 are likely due to chance since the levels of lead are somewhat lower than the earlier timeframes. However, no adjustments affected the odds of menopause associated with blood lead in a substantive way, particularly for the highest quartile of exposure. The finding is notable since the levels of lead observed in the current study are substantially lower (mean levels <2 ug/dL, 99th percentile = 6.7 ug/dL) than in prior studies and are well below the CDC level of concern (10 ug/dL).

5. Conclusions

All lead exposure is from external, environmental sources. We observed relatively low blood lead levels in this nationally-representative sample of US women at midlife, suggesting the lifetime accumulation of lead body burden in bone was generally low as well. Given that, and recognizing the limitations of this cross-sectional analysis, we nevertheless

found a strong and consistent relation between blood lead levels and the odds of natural menopause.

These data suggest that lead exposure, even at low levels, are associated with reproductive senescence. Evidence from non-human primates provide support for this hypothesis as does the hormonal profile changes in prepubertal girls and premenopausal women. Longitudinal studies with repeated lead and hormone measures around the menopausal transition are needed to clarify these relations and determine the contribution of lead to earlier age at menopause.

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Table 1

Characteristics of US women aged 45 to 55 who reported a natural menopause (yes) or had a menstrual period in the last year (no), National Health and Nutrition Examination Survey, 1999–2010.

Characteristic	Menopausal Status		
	Yes n=638	No n=1144	Total n=1782
Age in years (mean, se)	51.6 (0.1)	48.5 (0.1)	49.5 (0.1)
Blood lead ug/dL (geometric mean, se)	1.71 (0.04)	1.23 (0.02)	1.38 (0.03)
Race/ethnicity (% , se)			
White	70.5 (2.3)	74.7 (1.7)	73.3 (1.7)
Non-Hispanic Black	10.2 (1.3)	9.3 (0.9)	9.6 (0.9)
Mexican American	6.1 (0.9)	6.2 (0.6)	6.2 (0.6)
Others/Multiracial	13.2 (1.9)	9.7 (1.1)	10.9 (1.1)
Poverty (% , se)			
<100%	11.2 (1.4)	8.9 (0.9)	9.7 (0.9)
100% to 199%	12.9 (1.5)	12.9 (1.1)	12.9 (0.9)
200% or more	69.2 (2.4)	72.7 (1.8)	71.5 (1.5)
Smoking (% yes, se)	26.7 (2.1)	19.7 (1.7)	22.1 (1.4)
Current hormone replacement therapy (% , se)	13.9 (1.7)	5.2 (0.8)	8.2 (0.9)

Adjusted odds ratio (OR) and 95% confidence interval (95% CI) of having a natural menopause by quartile of blood lead among US women aged 45–55, National Health and Nutrition Examination Survey, 1999–2010.

Table 2

Lead Exposure Quartile	NHANES 1999–2010 n= 1782	NHANES 1999–2002 n=515		NHANES 2005–2008 n=541	
	OR (95% CI) ^a	OR (95% CI) ^a	OR (95% CI) ^b	OR (95% CI) ^a	OR (95% CI) ^c
Q1 (LOD to 1.0)	Reference	Reference	Reference	Reference	Reference
Q2 (1.0 to 1.4)	1.7 (1.0 – 2.8)	1.0 (0.3–3.5)	1.1 (0.3 – 3.9)	3.0 (0.9–9.8)	3.4 (0.9 – 12.2)
Q3 (1.4 to 2.1)	2.1 (1.2 – 3.6)	1.3 (0.4–4.5)	1.2 (0.3 – 4.7)	4.9 (1.5–16.1)	4.1 (1.1 – 15.2)
Q4 (2.1 to 22.4)	4.3 (2.6–7.2)	5.1 (1.4, 18.0)	4.2 (1.2 – 15.5)	10.5 (3.1–35)	9.7 (2.8 – 33)

^a Adjusted for age, race/ethnicity, current hormone replacement therapy, smoking and poverty

^b Adjusted for bone alkaline phosphatase, age, race/ethnicity, current hormone replacement therapy, smoking and poverty

^c Adjusted for femoral neck bone density, age, race/ethnicity, current hormone replacement therapy, smoking and poverty